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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,105	04/03/2001	Michael W. Russell	D6321	3233

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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	9

DATE MAILED: 05/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/825,105	RUSSELL ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6 and 24-29* is/are pending in the application.

4a) Of the above claim(s) *9-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6 and 24-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Applicants' response and amendment filed 2/24/03 have been entered as paper No. 8. Claims 4, 5, 7, and 8 have been canceled. Claims 1, 24, and 27 have been amended. Claims 1-3, 6, and 24-29 are under current examination.

This application contains claims (9-23) drawn to an invention nonelected without traverse in Paper No. 5. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6, and 24-29 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Toida et al* (Infect Immunity 1997;65:909-15), in view of *Rappuoli et al* (Immunol Today 1999 Nov;20:493-500), and further in view of *Schodel et al* (Infect Immunity 1989;57:1347-50; and Vaccine 1990;8:569-72) and *Connell et al* (Immunol Lett 1998;62:117-20; and Infect Immunity 1992;60:1653-61).

In paper No.8, applicants argue that the present invention focus on type II enterotoxins (LT-IIa and LT-IIb), whereas Toida and others studies Type I enterotoxins. Particularly applicants indicated that there are several structural differences between

type I and type II enterotoxins, and there is no nucleotide or amino acid homologies for the B polypeptides between Type I and Type II enterotoxins, therefore, in view of the significant structural and functional differences, one of ordinary skill in the art could not readily deduce immunomodulatory functions for one type of enterotoxin based on the properties of the other type without empirical experimentation. Applicants further argue that the combined teaching does not teach or suggest methods of inducing *cellular* immune response by a chimeric immunogen comprising subunits of type II entertoxin as claimed.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the present instance, as indicated in the previous Office action paper No. 6, *Toida et al* teach inducing immune response by administering intragastrically a chimeric protein (a fusion immunogen) comprising SBR-CTA2/B (A2 and B subunits of cholera toxin, abstract), wherein the immunization induces both antibodies in the serum (fig. 1), and T cell response including CD4+, and CD8+ cells (fig. 3). *Toida et al* do not teach LT-IIA2/B.

Rappuoli et al compare the differences between the CT and LT in structure and mucosal adjuvanticity including the difference in ganglioside-binding, and teach LT enterotoxin as a whole could activate both Th1 (cellular immune response) and Th2

cells (3rd paragraph, left column, page 499). *Rappuoli et al* do not distinguish the LT-II from LT-I enterotoxin.

Schodel et al teach using the subunit B of LT enterotoxin as adjuvant for immunization, and observed antibody, as well as T cell response to antigens in C57BL/10 mice. *Schodel et al* do not do not distinguish the LT-II from LT-I enterotoxin.

Connell et al teach both LT-I and LT-II heat-labile enterotoxin could be used as mucosal adjuvant, and that LT produced by *E. coli* and CT produced by *Vibrio cholerae* belong to a family of proteins that are related in structure and function. They compare the adjuvant effect of CT with LT-IIa mixed with an antigen of interest, fimbrillin, and concluded that LTIIa and CT are equally potent adjuvants in the rat model (fig. 2 and paragraph bridging pages 119-120). In another study, *Connell et al* compared different combinations of A and B subunits of LT-I and LT-II (tables 1, 2, 4), and concluded, "ALL HOMOLOGOUS AND HETEROLOGOUS COMBINATIONS OF A AND B POLYPEPTIDES FROM TYPE I AND TYPE II HEAT-LABILE ENTEROTOXINS ARE CAPABLE OF ASSEMBLING INTO ACTIVE HOLOTOXINS IN VIVO, ALTHOUGH NOT WITH EQUAL EFFICIENCY" (last paragraph). With regard to the structure-functional relationship of the B subunit of LT-I and LT-II, *Connell et al* teach, "THESE FINDINGS SUGGEST THAT TYPE I AND TYPE II ENTEROTOXINS HAVE CONSERVED STRUCTURAL FEATURES THAT *PERMIT* THEIR A AND B POLYPEPTIDES TO FORM HYBRID HOLOTOXINS, ALTHOUGH THE *B POLYPEPTIDES* OF THE TYPE I AND TYPE II ENTEROTOXINS *HAVE VERY LITTLE AMINO ACID SEQUENCE HOMOLOGY*" (Last sentence of the abstract). Apparently, it is well known in the art at the time of the instant effective filing date, that the structural difference of the B subunit does little toward the adjuvanticity of LT-II and LT-I.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Toida et al, Rappuoli et al, Schodel et al, and Connell et al* by selecting and combining an antigen of interest with an adjuvant of interest with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the method because it is known that CT as an adjuvant would induce a Th2 type of response whereas both LT-I and LT-II would not discriminate between the type of responses induced, it is within the knowledge of the ordinary skilled to determine which type of adjuvant should be used for the particular antigen of interest. Thus, the claimed invention as a whole was *prima facie* obvious.

The instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Given the teaching of the prior art using compositions of an immunogen of interest combined with a mucosal adjuvant of interest whether they are CT, LT-I, or LT-II-all taught to be useful for inducing humoral and cellular immune response, it would have been *prima facie* obvious to one of ordinary skill in the art to combine these compositions to generate a new composition for inducing an immune response with a reasonable expectation of success. Therefore, the rejection stands.

Claims 1-3, 6, and 24-29 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Russell et al* (US 6,030, 624), in view of *Rappuoli et al* (Immunol Today 1999 Nov;20:493-500), and further in view of *Schodel et al* (Infect Immunity 1989;57:1347-50; and Vaccine 1990;8:569-72) and *Connell et al* (Immunol Lett 1998;62:117-20; and Infect Immunity 1992;60:1653-61).

Applicants presented the same argument for this rejection as to the previous rejection. Thus, for reasons of the record and those presented in the immediate preceding section, this rejection stands.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The prior rejection of Claims 1-3, 6-8, and 24-29 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,030,624, in view of *Rappuoli et al* (Immunol Today 1999 Nov;20:493-

500), and further in view of *Schodel et al* (Infect Immunity 1989;57:1347-50; and Vaccine 1990;8:569-72) and *Connell et al* (Immunol Lett 1998;62:117-20; and Infect Immunity 1992;60:1653-61) is withdrawn in view of the amendment and argument.

No claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
May 1, 2003

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER